DEPARTMENT OF THE AIR FORCE
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28 June 2000

MEMORANDUM FOR US EPA
NCEA (MD-52)
RTP, NC 27711
ATTN: ANNIE M. JARABEK

FROM: Elaine Merrill
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SUBJECT: Consultative Letter, AFRL-HE-WP-CL-2000-0036, Human PBPK Model for Perchlorate Inhibition of Iodide Uptake in the Thyroid

1. A physiologically-based pharmacokinetic (PBPK) model was constructed to predict the inhibition of thyroid iodide uptake in humans after exposure to perchlorate (ClO_4). The model describes systemic clearance of perchlorate and radioiodide tracer into urine and concentrations in blood, skin, slowly perfused tissue, rapidly perfused tissue, gut and thyroid; inhibition of iodide uptake in the thyroid is also described. The skin, gut and thyroid compartments are comprised of two subcompartments in order to account for non-linear uptake of perchlorate and iodide into the tissues. Tissue/blood partition coefficients were obtained from published animal studies. Rate constants for the gut, thyroid and blood compartments were fitted using published measurements of radioiodide uptake in the thyroid, aspirated gastric secretions, serum and urine. Active uptake and passive diffusion rates for skin were estimated from radiolabeled perchlorate data in the rat. Systemic clearance of perchlorate was established by fitting both published and unpublished human serum and urinary excretion data. Thyroid radioiodide uptake measurements taken before and during perchlorate treatment were used to estimate the uptake of iodide and inhibition in the thyroid (see Attachment 1).

2. In general, the proposed model is able to describe serum levels and urinary excretion of perchlorate as well as the extent of inhibition in the thyroid. The model slightly overpredicted urinary excretion and slightly underpredicted plasma concentrations of perchlorate in repeated low dosing studies. Available human data for model development at this point were limited. Serum and urine samples from a recent comprehensive kinetic study conducted by Dr. Monte Greer and colleagues, Oregon Health Sciences University, Portland, OR, were not yet available

for incorporation into this report. The results will be used in future modeling efforts, which will focus on describing subsequent effects of iodide uptake inhibition on thyroid hormone synthesis and regulation.

3. For further information, please contact Dr. Kyung Yu, Project Manager or myself by phone: (937) 255-5150, fax: (937) 255- 1474 or e-mail: elaine.merrill@wpafb.af.mil.

Elaine A Merrill

ELAINE A. MERRILL
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Attachments:
1. Human PBPK Model for Perchlorate Inhibition of Iodide Uptake in the Thyroid Report
2. Human kinetic data from Dr. Georg Brabant (12 mg/kg-d and 1 mg/kg-d perchlorate)
3. Human kinetic data from Dr. Lewis Braverman (~0.14 mg/kg-d perchlorate)

1st Ind, AFRL/HEST 28 June 2000

MEMORANDUM FOR US EPA
ATTN: MS. ANNIE JARABEK

This letter report has been coordinated at the branch level and is approved for release.

David R. Mattie

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Human PBPK Model for Perchlorate Inhibition of Iodide Uptake in the Thyroid

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28 June 2000

INTRODUCTION

Perchlorate is not metabolized and is rapidly excreted in urine; however, while in the body perchlorate competitively inhibits iodide uptake in the thyroid and other tissues. For that reason, perchlorate has been used therapeutically to treat hyperthyroidism (Wolff, 1988). If administered within hours of an accidental or excessive exposure to radioiodide, it can serve as a safe and effective prophylaxis (thyroid uptake blocking agent) (Ribela *et al.*, 1999). Commercially, the salt (ammonium perchlorate) is used, for its strong oxidizing properties, in rocket fuel and fireworks. Perchlorate contamination has been recently detected in several water sources (Urbansky and Schock, 1999). As a result, there's concern that chronic exposure to low levels in drinking water could lead to hypothyroidism.

Few studies have been conducted on the kinetics of perchlorate in either humans or animals. However, information was available on the distribution of iodide and perchlorate in rats and rabbits. Higher than serum concentrations of iodide and perchlorate have been noted in the thyroid, adrenal glands, bile, spleen, gastric mucosa, salivary glands, ovaries, testes and kidneys (Anbar *et al.*, 1959; Perlman *et al.*, 1941; Durand, 1938). The tissue to plasma iodide ratio is greatest in the thyroid. The ability of the thyroid to transport and concentrate iodide from plasma is necessary for thyroid hormones synthesis.

Iodide is actively transferred into the thyroid by the sodium-iodide symporter (NIS), a membrane protein that resides in the basolateral membrane of thyroid epithelial cells. Abnormalities in expression or function of the symporter can lead to thyroid disease (Spitzweg, 2000). The NIS simultaneously transports both Na^+ and I^- ions from extracellular fluid (plasma) into the thryoid epithelial cell. This process is an example of secondary active transport. Energy is provided by the electrochemical gradient of sodium across the cell membrane; the low intracellular concentration of sodium is maintained by sodium-potassium pumps (Ajjan *et al.*, 1998).

The presence of NIS is an indicator of active uptake for iodide. NIS is highly expressed in thyroid epithelial cells. Lower levels of expression have been detected in the mammary gland, salivary gland, skin, stomach and colon. However, only the thyroid has been found to organify iodide (Ajjan *et al.*, 1998; Spitzweg *et al.*, 1998). The most important stimulator of symporter gene and protein expression is thyroid-stimulating hormone (TSH), similar to what is observed with other important thyroid proteins such as thyroglobulin and thyroid peroxidase (Spitzweg *et al.*, 1998).

The proposed model describes active uptake of iodide and perchlorate in gastric juice, thyroid and skin, as well as venous equilibrium with slowly and rapidly perfused tissue. Perchlorate's transport mechanisms can be modeled in the same manner as iodide, as it binds to the NIS and competitively inhibits iodide uptake (Anbar *et al.*, 1959; Brown-Grant and Pethes, 1959). The kinetics of these anions differ in that iodide is organified in the thyroid (thyroid hormone production) whereas perchlorate is thought to be unreactive and eventually diffuses from the thyroid into systemic circulation. Although perchlorate is quickly eliminated unchanged in the

urine (Wolff, 1998), the impact of chronic displacement of iodide from prolonged exposure to perchlorate-contaminated drinking water is the focus of this and ongoing modeling efforts.

The objective of this effort is to simulate serum perchlorate and iodide levels and the subsequent inhibition of iodide uptake into the thyroid. Results are based on fits of available data. The model does not include effects on thyroid hormone production and homeostasis at this point.

METHODS

The data used in model development were obtained from several published human studies (Eichler, 1929; Kamm and Drescher, 1973; Durand, 1938; Hays and Solomon, 1965) and two recent unpublished human studies. The two recent studies were conducted by Drs. Holger Leitolf and Georg Brabant of the Medizinische Hochschule, Hanover, Germany, and Dr. Lewis Braverman of Brigham and Women's Hospital, Boston, MA.

1. Human Iodide Kinetic Data

Probably the most comprehensive study available in the published literature on early iodide distribution was reported in 1965 by Hays and Solomon. The authors studied the effect of gastrointestinal cycling on iodide kinetics in nine healthy males after an intraveneous (*iv*) dose of 3.44×10^{-3} ng ^{131}I /kg. Frequent measurements of radioiodide uptake in the thyroid, gastric secretions, plasma and cumulative urine samples were taken during the three hours following injection. Gastric secretions were collected using a nasogastric tube with constant suction while the subjects remained in a resting position (only standing to urinate). Saliva was not collected separately and therefore pooled, to some extent, with gastric juices. To account for the removal of gastric iodide from circulation and determine its impact on free iodide distribution, a control session was run on the same subjects without aspiration of gastric secretions. Aspirated gastric secretions accounted for 23% of the ^{131}I administered.

2. Human Perchlorate Kinetic Data

Three published studies reported cumulative urine concentrations collected from healthy males after receiving a single high oral dose of perchlorate (Durand, 1938; Kamm and Drescher, 1973; Eichler, 1929). Oral doses administered in these studies were 784 mg $NaClO_4$ (635 mg ClO_4 = 9.07×10^6 ng/kg for a 70 kg male) (Durand, 1938); 1000 mg $NaClO_4$ (765 mg ClO_4 = 9.56×10^6 ng/kg) (Kamm and Drescher, 1973) and 2000 mg $KClO_4$ (1400 mg ClO_4 = 2.0×10^7 ng/kg for a 70 kg male) (Eichler, 1929). The studies did not include simultaneous serum perchlorate levels. The first order elimination constant for perchlorate (KUc_p) values were determined by fitting the cumulative amount of perchlorate in urine.

Both urine and serum perchlorate concentrations were obtained from a recent unpublished study by Drs. Brabant and Leitolf of Medizinische Hochschule, Hanover, Germany. In their study, 7

healthy males ingested 12.0 mg/kg-d perchlorate dissolved in 1 liter of drinking water for 2 weeks. The daily perchlorate dose was divided equally in three portions and ingested three times per day (approximately between 6 and 8 am, 11 am and 1 pm and 6 and 8 pm). Blood and 24-hour (h) urine specimens were collected on days 1, 7 and 14 of perchlorate treatment and on the proceding two mornings after perchlorate administration was discontinued. One additional male subject was given 1 mg/kg-d, following the same dosing regime. Serum and urine samples were analyzed for perchlorate at the Operational Toxicology Branch, Human Effectiveness Directorate at the Air Force Research Laboratory (AFRL/HEST), Wright Patterson Air Force Base (WPAFB), OH. TSH, thyroid hormones and thyroglobulin analyses were also performed on serum at the Medizinische Hochschule.

3. Human Perchlorate Kinetics and Inhibition of Thyroid Uptake Data

Another recent unpublished study was performed by Dr. Braverman of Brigham and Womens's Hospital, Boston, MA. Braverman studied the effect of low doses of perchlorate on thyroid function. Nine healthy male volunteers, with no signs or symptoms of thyroid disorders, ingested 10 mg/day perchlorate dissolved in 1 liter of water for 14 days. The dose equated to approximately 0.14 mg/kg-d for a 70 kg male. Subjects ingested the solution intermittently throughout the day. Exact ingestion times were not available. For simulation purposes, a reasonable assumption was made that each subject consumed the perchlorate drink four times per day during the waking hours.

Baseline blood and 24-h urine collections were taken before perchlorate treatment, between 8 and 9 am, on days 7 and 14 of perchlorate ingestion and again 14 days after the last day of perchlorate ingestion. Four-, eight- and 24-h thyroid ^{123}I uptake (RAIU) were taken one to two days previous to perchlorate treatment (baseline), on day 14 of perchlorate exposure and 14 days after perchlorate.

Serum and urine samples, obtained from the unpublished studies described above, were analyzed for perchlorate at AFRL/HEST using the analytical methods below. Serum samples had also been analyzed for iodine and thyroid function tests at the hospital.

Analytical Methods

Serum samples were analyzed for perchlorate by ion chromatography on a Dionex DX-500 ion chromatography system with a GP-40 Gradient Pump, CD-20 Conductivity Detector, a LC-20 Chromatography Enclosure and an AS40 Automated sampler. The injection volume was 200 µL. Anion separation was obtained on a Dionex Ion Pac AS-11, 2.0 x 250-mm separation column with an AG-11 2.0 x 50 mm guard column and an ATC-1 anion trap column. The mobile phase consisted of 80 mM NaOH. The mobile phase flow rate was set at 0.25 mL/min. Background suppression was achieved by using an Anion Self-Regenerating Suppressor (ASRS)-ULTRA suppressor, with external water flowing at 10 mL/min.

For sample preparation, 50 µL of serum was precipitated with 200 µL of cold 100% ethanol. Samples were then centrifuged at 14,000 rpm for 30 minutes, using an Eppendorf microcentrifuge. The supernatant was removed and evaporated to dryness under the flow of nitrogen gas. Samples were then reconstituted in 1 mL of 18 MΩ/cm water. The reconstituted samples were filtered through a Millipore Millex HV-13 0.45 micron syringe filter and placed in 2 mL sample vials for analysis. The samples required no further dilution, making the final dilution after preparation 1:20. To check the performance of the instrument a duplicate sample, a perchlorate spiked sample and control standards were evaluated after every ten serum samples.

Ion chromatography of urine was performed on a Dionex DX-500 microbore ion chromatograph system with a GP-40 Gradient Pump, CD-20 Conductivity Detector, an LC-20 Chromatography Enclosure and an AS40 Automated sampler. The injection volume was 200 µL. Anion separation was obtained on a Dionex IonPac AS-11 2.0 x 250-mm separation column with an AG-11 2.0 x 50 mm guard column and an ATC-1 anion trap column. The mobile phase varied from 60 to 120 mM NaOH, depending on the sample. The mobile phase flow rate was set at 0.25 mL/min. Background suppression was achieved by using an Anion Self-Regenerating Suppressor (ASRS)-ULTRA suppressor, with external water flowing at 10 mL/min.

For the sample preparation of urine, 500 µL of urine was filtered through a Millipore Millex HV13 0.45 micron syringe filter. The sample was then placed in a Millipore Ultrafree 0.5 centrifuge filter and was centrifuged in an Eppendorf microcentrifuge at 14,000 rpm for 30 minutes. The filtered sample was then removed and diluted 1:500 in 2 mL sample vials. The samples in which no perchlorate was detected were prepared a second time, using the same process as described above, but diluted only 1:50. If there was still no perchlorate detected in the samples, the samples were prepared with the same method as above and diluted 1:25. A 1:25 dilution is the lowest dilution that can be used without producing a significant increase in baseline noise and a subsequent decrease in detection capabilities.

PBPK Model Development

The development of the current human perchlorate and iodide model was based largely upon the published data mentioned previously and attempts to describe the distribution of iodide in animals and humans. Tissues, reported to have tissue/plasma iodide concentrations greater than one and in which there were either human or animal kinetic data available, were depicted as compartments of nonlinear uptake.

Two five-compartmental PBPK sub-models were used to describe the disposition of radioiodide tracer and perchlorate in thyroid, gastrointestinal tract, skin and slowly and rapidly perfused tissues (Figure 1). The gut, skin and thyroid are each comprised of a tissue and plasma compartment to describe non-linear uptake of the iodide and perchlorate anions. The blood compartment is composed of plasma and red blood cells (RBCs). The free anions in plasma are available for diffusion and active uptake into tissues.

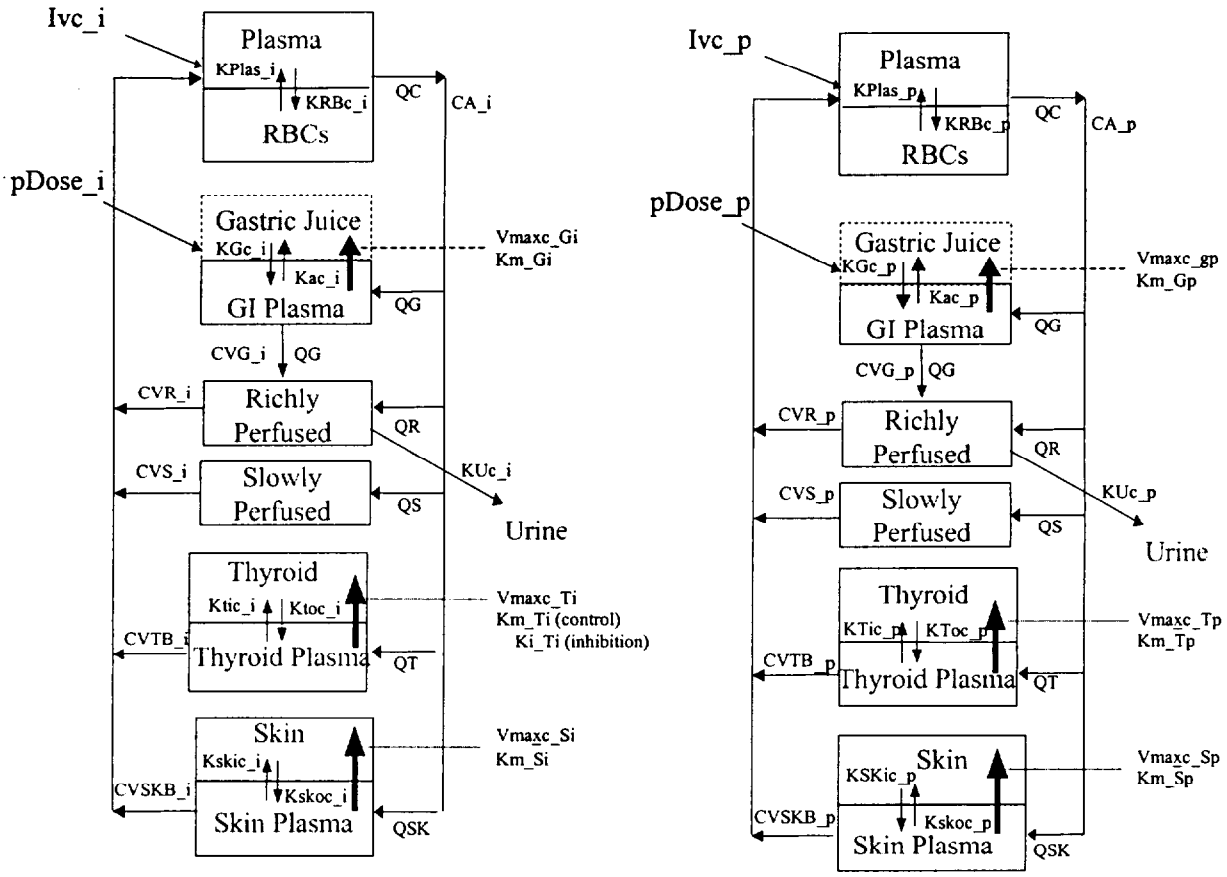

Figure 1. Schematic of human PBPK model for perchlorate and iodide distribution. Bold arrows indicate active uptake at NIS sites, whereas small arrows indicate passive diffusion. Inhibition of total thyroidal iodine uptake is indicated by the change in the control thyroid affinity constant, Km_Ti, to Ki_Ti.

Although other tissues have been found with iodide concentrations greater than that of plasma (e.g., salivary glands) (Honour *et al.*, 1952), these tissues were lumped with slowly and rapidly perfused tissues in an effort to keep the model simple. The iodide pools of these tissues are expected to be too small to significantly affect plasma inorganic iodide levels. The similar size of iodide and perchlorate and affinity for NIS allowed parameter values for iodide to be used interchangeably with those of perchlorate and vise versa, when chemical-specific data were not available.

Physiological Parameters

Human tissue volumes and blood flows were obtained from the literature (Table 1). Considerable variability was reported for some parameters. For example, blood flow to the gastrointestinal (GI) tract can increase tenfold in response to enhanced functional activity

(secretion and digestion) (Granger *et al.*, 1985). Blood flows used in the model represent estimates of resting values.

TABLE 1. PHYSIOLOGICAL PARAMETERS

Parameter	Value	References
Volumes		
Plasma V*plasc* (%BW)	4.4	Marieb, 1992
RBCs *VRBCc* (%BW)	3.5	Marieb, 1992
Thyroid *VTc* (%BW)	.03	Yokoyama *et al.*, 1986
Thyroid Capillary Blood *VTBc* (%VT)	18.1	18.1% thyroid weight in rat (Brown *et al.*, 1997)
Skin *VSkc* (%BW)	3.7	Brown *et al.*, 1997
Skin Capillary Blood *VSkBc* (%VSk)	8.0	Brown *et al.*, 1997
Gut (without contents) *VGc* (%BW)	1.7	Brown *et al.*, 1997
Gut Capillary Blood *VGBc* (%VG)	2.9	Rat intestine (Altman and Dittmer, 1971b)
Slowly Perfused *VSc* (%BW)	70.3	Lumped compartment
Richly Perfused *VRc* (%BW)	11.0	Lumped compartment
Blood Flows		
Cardiac Output *QCc* (L/h/kg)	16.5	Davis and Mapleson, 1981
Thyroid *QTc* (%QC)	9.3	Tegler *et al.*, 1976
Gut *QGc* (%QC)	17.1	Davis and Mapleson, 1981
Skin *QSKc* (%QC)	5.8	Brown *et al.*, 1997
Slowly Perfused *QS* (%QC)	8.9	Lumped compartment
Richly Perfused *QR* (%QC)	58.9	Lumped compartment

Thyroid volume was obtained from a study by Yokoyama *et al.* (1986) involving ultrasound measurements on 57 healthy volunteers (11 males and 46 females, 37 to 74 years of age). Subjects had no signs, symptoms or history of thyroid disorders. Their serum levels of T_3, T_4, free T_4 and TSH were within normal ranges. The mean thyroid volume was 13.4 ± 4.1 mL and mean thyroid volume to body weight ratio was 0.251 ± 0.074 mL/kg [mean ± standard deviation (s.d.)], approximately 0.03% of body weight (BW). A positive correlation between thyroid volume and both body weight and age was demonstrated with weight having the most pronounced influence. Human thyroid capillary bed volume (VTBc) was not available in the

literature. Therefore, the volume (%BW) of the thyroid capillary bed in the rat was used (Table 1).

Despite its small size, blood flow to the thyroid is relatively high. Tegler *et al.* (1976) measured thyroid blood flow (QTc) in 12 normal subjects using an electromagnetic meter and a probe applied to an inferior thyroid artery. Measurements were made over one hour. Mean blood flow through one artery was 6.4 ± 3.0 mL/min (mean ± s.d.). The authors assumed that the blood flow of the entire thyroid gland (on the basis of changes in the color after occlusion of one thyroid artery) to be four times the average flow measured in one artery (approximately 9.3% of cardiac output, Table 1).

Mean volumes of human gastric contents at rest were not readily available in the literature. This parameter is highly variable and therefore not defined in the model. The human gut volume without contents (1.7% BW) was provided in Brown *et al.* (1997). Human data on the gut capillary bed volume (VGBc) were not found in the published literature. A value was derived from rat intestine data (Altmann and Ditter, 1971) (Table 1). Since volume was not available for gut contents, the model predicts the masses of radioiodide and perchlorate in gastric juices, but not concentrations.

Partitioning Coefficients

Partition coefficients for iodide and perchlorate were estimated from *in vivo* studies. Tissue:plasma ratios were determined during the terminal phase of clearance from plasma. Halmi *et al.* (1956) measured organ:serum concentration ratios for radioiodide in rats approximately 1, 4 and 24 h after an *iv* dose of the tracer iodide. The average liver:serum and muscle:serum iodide ratios at approximately 4 h after an injection of ^{131}I (0.40 and 0.21, respectively) were used to represent human rapidly and slowly perfused partitioning coefficients for iodide (Table 2). Perlman *et al.* (1941) reported similar iodine ratios in rabbit tissues at 5 h after subcutaneous dosing with NaCl and a tracer amount of iodide (0.44 for liver/blood and 0.19 for muscle/blood). The liver:blood and muscle:blood ratios remained relatively constant for up to 96 hours.

Perchlorate partition coefficients for rapidly (0.74) and slowly perfused (0.27) tissues were derived from rat studies, 24 hours after a single *iv* dose of 3.3 mg $^{36}ClO_4$/kg (Fisher *et al.*,2000) (Table 2). Anbar *et al.* (1950) reported liver:blood and muscle:blood ratios of 0.38 and 0.12, respectively, in rabbits 12 hours after an intraperiteneal (*ip*) dose of 100 mg $KClO_4$.

Affinity Constants and Maximum Velocities

Gluzman and Niepomniszcze (1983) derived a mean Michaelis-Menton affinity constant (Km) of 3.96×10^6 ng/h/kg-BW from thyroid slices of 5 normal individuals; the thyroid slices were incubated with several medium iodide concentrations. The authors noted little variation between thyroid specimens of different species. Wolff (1998) noted that the Km for perchlorate and other

similar monovalent anions do not differ greatly from iodide. However, the maximum velocity term (Vmax) did vary between tissues. Therefore, the same Km value was assumed to described the affinity of both iodide and perchlorate in thyroid, gastric juices and skin (Table 2), while Vmax values were fitted to experimental data for either iodide or perchlorate in each tissue.

Fitting Model Parameters to Observed Data

Parameter terminology used in this model is summarized in Table 2. Simultaneous differential equations, which simulate radioiodide and perchlorate distribution in the proposed mathematical model, were written and solved using ACSL (Advanced Continuous Simulation Language) software (Pharsight Corp., Mountain View, CA).

The basic equation used to simulate active uptake of iodide and perchlorate alone (without accounting for inhibition) in tissues with NIS activity is:

$$\frac{dAX\_y}{dt} = \frac{V\max\_Xy \times CVX\_y}{Km\_Xy + CVX\_y}$$

where:

AX_y = Amount of y^{th} anion in X^{th} tissue (ng)
t = Time
Vmax_Xy = Maximum uptake of y^{th} anion at X^{th} tissue's symporter (ng/h)
Km_Xy = Michaelis-Menton affinity constant for y^{th} anion in X^{th} compartment (ng/L)
CVX_y = Concentration of y^{th} anion in venous capillary blood of X^{th} compartment (ng/L)

Accounting for inhibition of active uptake of either iodide or perchlorate in the presence of the competing anion is expressed as:

$$\frac{dAX\_y}{dt} = \frac{V\max\_Xy \times CVX\_y}{Km\_Xy \times \left(1 + {CVX\_z}/{Km\_Xz}\right) + CVX\_y}$$

where:

Km_Xz = Michaelis-Menton affinity constant for z^{th} anion in X^{th} compartment (ng/L)
CVX_y = Concentration of z^{th} anion in venous capillary blood of X^{th} compartment (ng/L)

With the exception of the skin compartment, maximum capacities (Vmaxc_Xy) and first order rate constants describing passive diffusion (KXc_y) for other compartments were derived by fitting the model prediction to radioiodide (^{131}I) data by Hays and Solomon (1965). The aspirated secretions collected in that study, accounting for 23% of the dose, resulted in slightly

lower levels of radioiodide in the thyroid, plasma and urine than seen in the control session. No studies measuring perchlorate in gastric juice were found in the literature.

Data on radioiodide or perchlorate uptake into human skin were not available. The maximum capacity (Vmaxc_Sp) and first order diffusional rate constants (KSKic_p and KSKoc_p) used for the skin compartment were derived from data on $^{36}ClO_4$ uptake in adult male rat skin (Fisher *et al.*, 2000) (Table 2). It was assumed that, due to its large volume, skin represents a reasonable pool for slow turnover of iodide and perchlorate in human adults.

Rapid equilibrium of iodide between erythrocytes and plasma is supported by the work by Rall *et al.* (1950). Venous blood was drawn from normal individuals and immediately heparinized. Various amounts of labeled sodium iodide (0.1 to 0.3 mL) were added to 25 mL of blood and mixed for 20 minutes. The ratio of iodide concentration in erythrocytes to that in plasma was 0.67. When results were calculated on the basis of cell water content of 65% and plasma water content of 93%, the distribution of iodide between cells and plasma was approximately unity (0.96). Therefore, simulated curves representing RBC concentrations of either anion were fitted to plot parallel with observed plasma concentrations. Body weights, urinary excretion rate constants (Kuc), thyroid maximum velocities (Vmaxc) and inhibition affinity constants (Km) were fitted individually due to the innate variability of these parameters between human subjects.

TABLE 2. CHEMICAL SPECIFIC PARAMETERS

Partition Coefficients[a] (unitless)	**Iodide**	**Perchlorate**	**Source**
Slowly perfused / plasma *PS_*	0.21	0.31	Iodide – (*Halmi et al., 1956)* ClO_4 – *in vivo* $^{36}ClO_4$ study (Fisher *et al.*, 2000)
Rapidly perfused / plasma for ClO_4 *PR_*	0.80	0.56	Iodide – (Halmi *et al.*, 1956) ClO_4 – *in vivo* $^{36}ClO_4$ study (Fisher *et al.*, 2000)
***Max Capacity, Vmaxc* (ng/h/kg)[a,b]**	**Iodide**	**Perchlorate**	**Source**
Thyroid *Vmaxc_T*	3.0E5 to 7.6E5	3.0E5	Estimated, based on human radioiodide uptake (Hays and Solomon, 1965)
Skin *Vmaxc_S*	1.0E7	1.0E7	*in vivo* $^{36}ClO_4$ studies (Fisher *et al.*, 2000)
Gut *Vmaxc_G*	3.8E4	3.8E4	Estimated, based on radioiodide in gastric juice (Hays & Solomon, 1965)
Affinity Constants, $Km^{a,b}$ (ng/L)	**Iodide**	**Perchlorate**	**Source**
Thyroid *Km_T*	3.96E6	3.96E6	Gluzman & Niepomniszcze, 1983
Skin *Km_S*	3.96E6	3.96E6	Gluzman & Niepomniszcze, 1983
Gut *Km_G*	3.96E6	3.96E6	Gluzman & Niepomniszcze, 1983
First Order Rate Constants, $K^{a,b}$ (/h-kg)	**Iodide**	**Perchlorate**	**Source**
Oral absorption *Kac*	20.0	20.0	Fitted
Urinary excretion *KUc*	0.25 to 1.1	0.25 to 1.1	Fitted
Thyroid blood to thyroid *KTic*	0.0	0.0	Fitted
Thyroid to thyroid blood *KToc*	0.6	0.6	Fitted
Gut wall to gut blood *KGc*	200.0	200.0	Fitted
Bi-directional – plasma to RBC's *KRBC*	15.0	15.0	Fitted
Skin blood to skin *KSKic*	60	60	*In vivo* $^{36}ClO_4$ studies (Fisher *et al.*, 2000)
Skin to skin blood *KSKoc*	100	100	*in vivo* $^{36}ClO_4$ studies (Fisher *et al.*, 2000)

Notes: **a.** All parameters listed are notated in the model by either an i (for iodide) or p (for perchlorate) following the parameter name (e.g., PR_i, PR_p, Vmaxc_Ti, Vmaxc_Tp, etc.).

b. Vmaxc's and first order rate constants are scaled by BW as follows:

$$V\max\_Xy = V\max c\_Xy \times BW^{3/4} \quad \text{and}$$

$$KX\_y = KXc\_y / BW^{1/4}$$

where: X = compartment of concern (eg., G for gut, T for thyroid, etc.)
y = anion of concern (i for iodide, p for perchlorate)

RESULTS

1. Iodide Model

Early iodide kinetics were established by fitting data from Hays and Solomon (1965), as described above. The absorption constant (Kac_i) is the diffusional rate constant of free ^{131}I in gut plasma that is rapidly absorbed by the gut wall into gastric juice as shown in Figure 1. KGc_i refers to the rate constant of ^{131}I transfer from the gastric juice into the gastrointestinal plasma (Figure 1). To simulate the aspiration session, Kac_i was set to zero (Figure 2C), mathematically removing the amount absorbed by the gut from circulation. This approach accounts for the 23% of the ^{131}I dose removed from circulation during aspiration (Figures 2A through D). The maximum capacity in the thyroid (Vmaxc_Ti) and gut (Vmaxc_Gi) were then obtained by fitting values of ^{131}I uptake into the thyroid and gastric juice from the aspiration session. Vmaxc_Gi and Vmaxc_Ti were fit at $3.8x10^4$ and $3.0x10^5$ ng/h/kg, respectively (Figures 2B and C). KGc_i was fit to the linear curve of total ^{131}I in the aspirated gastric secretions at 200 /h (Figure 2C). The first order urinary excretion constant (KUc_i) was then fitted to simulate both cumulative urine content and plasma iodide (Figures 2A and D), resulting in a KUc_i value of 1.0 /h-kg (Table 2).

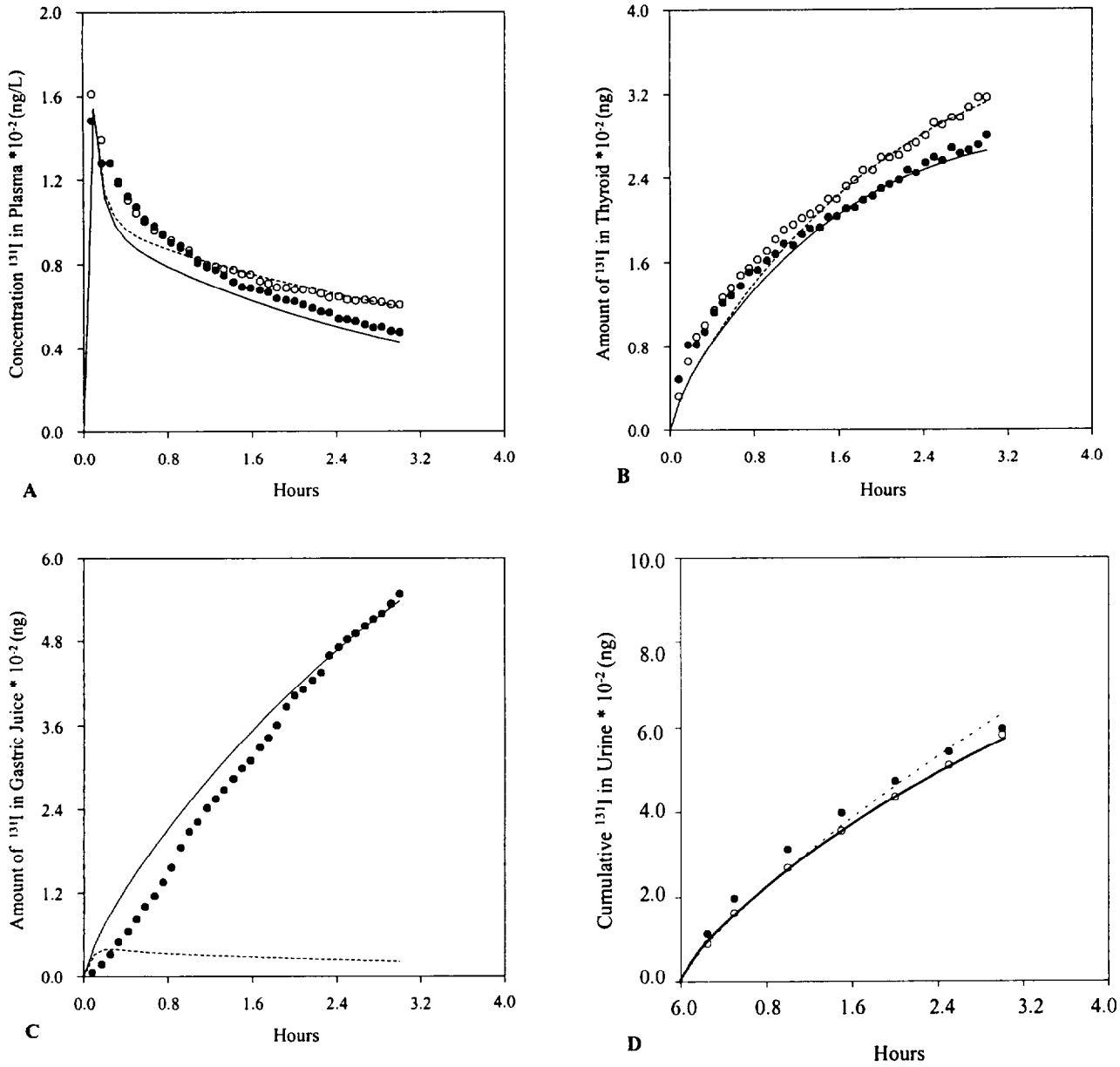

Figure 2. Mean ^{131}I in plasma (A), thyroid (B), gastric juice (C) and urine (D) of nine healthy males after an *iv* dose of 10 μCi ^{131}I (approximately 3.44x10^{-3} ng ^{131}I/kg) (Hays and Solomon, 1965). Solid lines and closed circles indicate model predicted and observed ^{131}I levels from aspiration session. Dashed lines and open circles indicated model predicted and observed values from the control session.

After fitting Vmaxc_Ti, Vmaxc_Gi, KGc_i and KUc_i to the aspiration session data, the corresponding control session data sets could all be predicted by simply setting the gastric absorption constant, Kac_i, to 20 /h. Then the model predicted the corresponding difference in

^{131}I levels in the thyroid, plasma and urine seen in the control session versus the aspiration session. (Figures 2A through D).

Interestingly, the simulated amount of ^{131}I in gastric juice (simulated control session) indicates that although there is very rapid uptake of iodide and perchlorate into the gastric juice, it is quickly reabsorbed (Figure 2C). GI clearance of iodide appears to be rapid and plays an important role in radioiodide conservation.

Hays and Wegner (1965) reported an iodide equilibrium between plasma and red blood cells (RBCs) occurring within three minutes. Therefore diffusion constants between red blood cells and plasma, KRBC_i and Kplas_i (Table 2), were fitted so that the predicted curves of both plasma and RBCs iodide concentrations simultaneously paralleled each other.

The model predictions suggest that during early iodide distribution there may be some loss of iodide from the thyroid. Figure 3 demonstrates the model simulation of active iodide uptake in the thyroid, with and without a first order rate loss by passive diffusion (Ktoc_i = 0.6 /h) and with Vmaxc_Ti = 3.0E5 ng/h/kg and Km_Ti = 3.96E6 ng/L. Without loss of ^{131}I through passive diffusion, the model overpredicts later timepoints

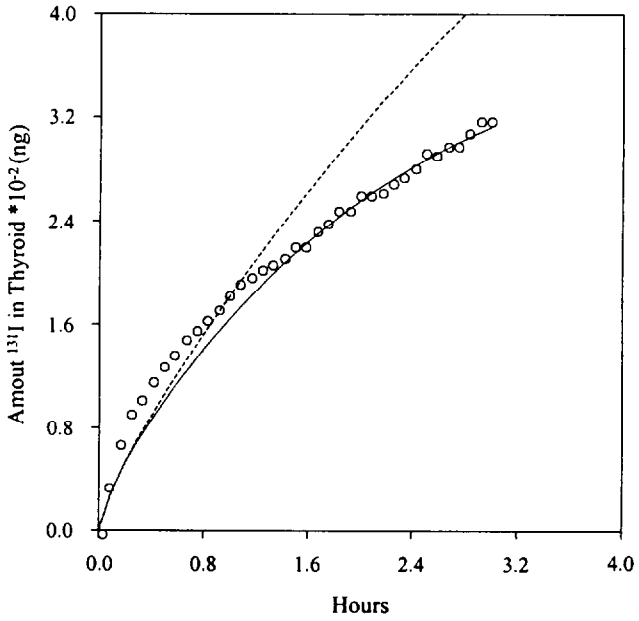

Figure 3. Amount of ^{131}I in thyroid from control session. Dotted line represents model prediction with no loss from thyroid to thyroid capillary blood. Solid line represents simulation of thyroid uptake assuming some diffusion of ^{131}I from the thyroid. Open circles indicate observed measurements (Hays and Solomon, 1965).

2. Perchlorate Model

Due to the lack of human data regarding uptake of perchlorate into specific tissues, the rate constant values for ^{131}I, described above, were applied to perchlorate (Table 2). Using these values, the model accurately simulated perchlorate measurements in urine (Figures 4 through 6). Cumulative urine concentrations were obtained from three published studies using therapeutic perchlorate dose levels. Oral doses administered in these studies were 784 mg $NaClO_4$ (635 mg $ClO_4 = 9.07x10^6$ ng/kg for a 70 kg male) (Durand, 1938), 1000 mg $NaClO_4$ (765 mg $ClO_4 = 9.56 \times 10^6$ ng/kg) (Kamm and Drescher, 1973) and 2000 mg $KClO_4$ (1400 mg $ClO_4 = 2.0x10^7$ ng/kg for a 70 kg male) (Eichler, 1929). The cumulative ClO_4 in urine from the Kamm and Drescher and the Eichler study were fit by applying a first order urinary elimination constant (KUc_p) of 1.0 /h. The KUc_p value for the Durand data was 1.1 /h.

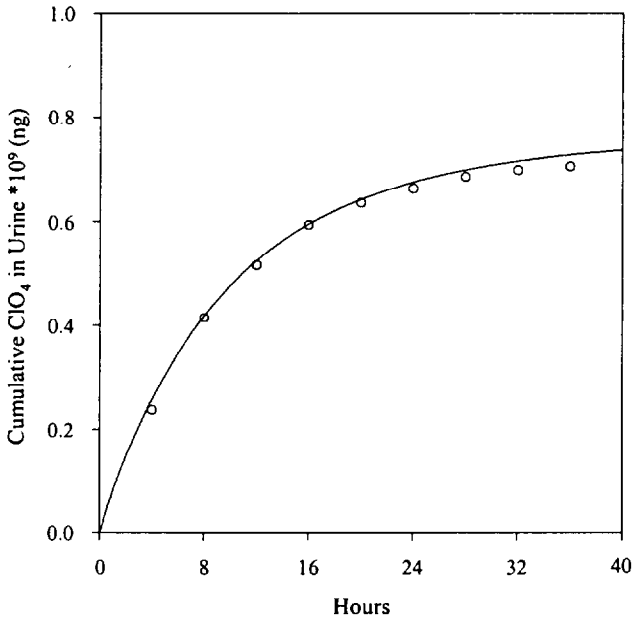

Figure 4. Model predicted (line) and observed (circles) cumulative amount of ClO_4 in urine from a healthy male orally dosed with 9.56 x 10^6 ng ClO_4 (Kamm and Drescher, 1973) with Kuc_p = 1.0 /h

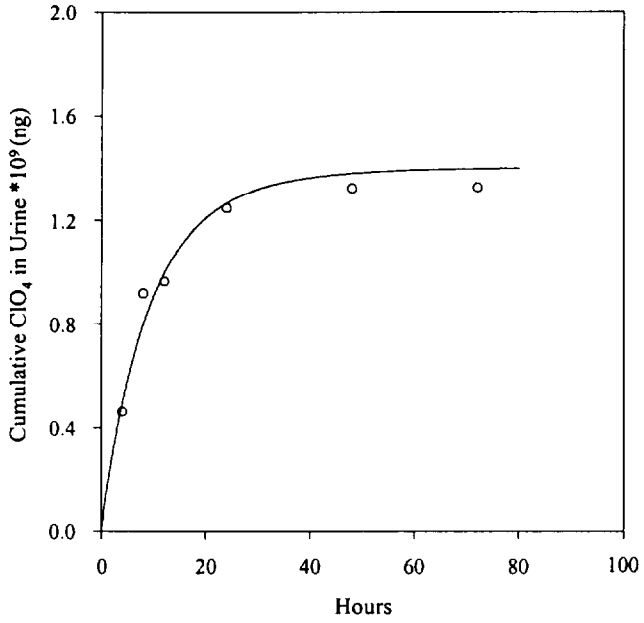

Figure 5. Model predicted (line) and observed (circles) cumulative amount of ClO_4 in urine from a healthy male orally dosed approximately $2.0x10^7$ ng ClO_4/kg (20 mg ClO_4/kg) (Eichler, 1929) with Kuc_p of 1.0 /h

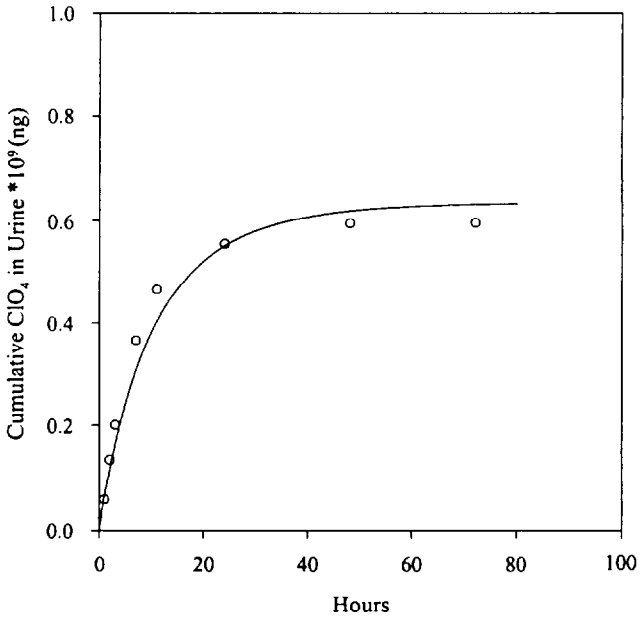

Figure 6. Model predicted (line) and observed (circles) cumulative amount of ClO_4 in urine from a healthy male orally dosed approximately 9.07×10^6 ng/kg ClO_4 (Durand, 1938) with Kuc_p of 1.1 /h

Using the constants derived from fitting Hays' and Solomon's early iodide distribution data shown in Table 2, serum perchlorate concentrations and urinary perchlorate excretion rates obtained from the unpublished Brabant and Leitolf study (described in the Methods section) were also simulated. Kuc_p values, individually fitted to simulate urinary excretion rates and serum concentrations, ranged from 0.4 to 1.1 /h (mean = 0.8 /h) (Table 3). Figure 7A presents the simulated and observed (mean ± s.d.) serum perchlorate concentrations based on the average BW and Kuc_p in Table 3. Because 24-h urine voids were collected on days 1, 7 and 14 of perchlorate exposure only and not on subsequent days, the cumulative amount of perchlorate in urine over the entire study period could not be evaluated. Instead urinary perchlorate excretion rates were established by dividing the amount of perchlorate accumulated in each 24-h void by 24. A slight increase was noted in the urinary perchlorate excretion rate, which was not predicted by the model (Figure 7B). In addition, plasma perchlorate clearance appeared slightly slower than predicted (Figure 7A).

TABLE 3. INDIVIDUAL PARAMETERS (12.0 mg ClO_4/kg-d DOSE GROUP)

Subject	BW (kg)	KUc_p (/h)[a]
1	70.0	1.1
2	69.0	0.6
3	99.0	0.4
4	84.0	0.9
5	77.0	1.0
6	115.0	1.0
7	71.0	0.9
Average	**83.6**	**0.8**

[a]KUc_p – fitted to serum perchlorate levels (unpublished data by Brabant and Leitolf)

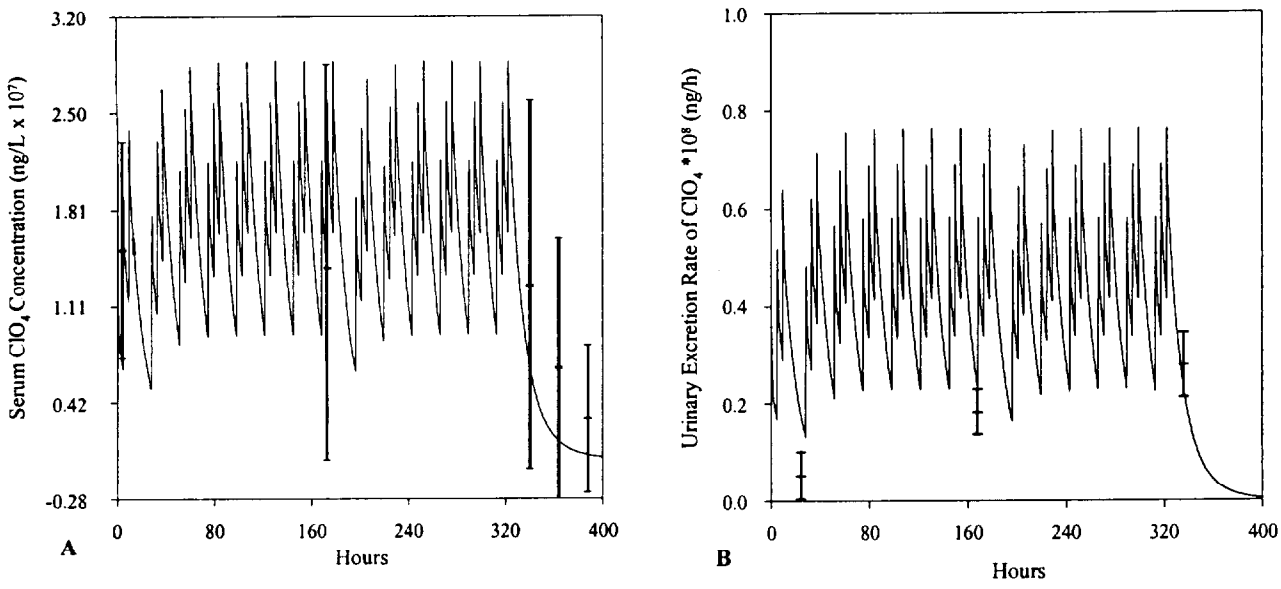

Figure 7. PBPK model predicted (solid lines) and actual mean values ± s.d. (bars) for serum concentrations (A) and urinary excretion rates (B) from 7 healthy males dosed with 12.0 mg/kg/d ClO_4, 3 times daily for 2 weeks. Simulations are based on the average Kuc_p presented in Table 3.

Brabant and Leitolf dosed an additional male volunteer with 1.0 mg/kg-d perchlorate in 1 liter of drinking water following the same dosing schedule as the 12 mg/kg-d group. The model simulations and observed data for serum levels and urinary excretion rates are presented in Figures 8A and B. Urinary excretion and serum levels were fit using a KUc_p of 0.9 /h.

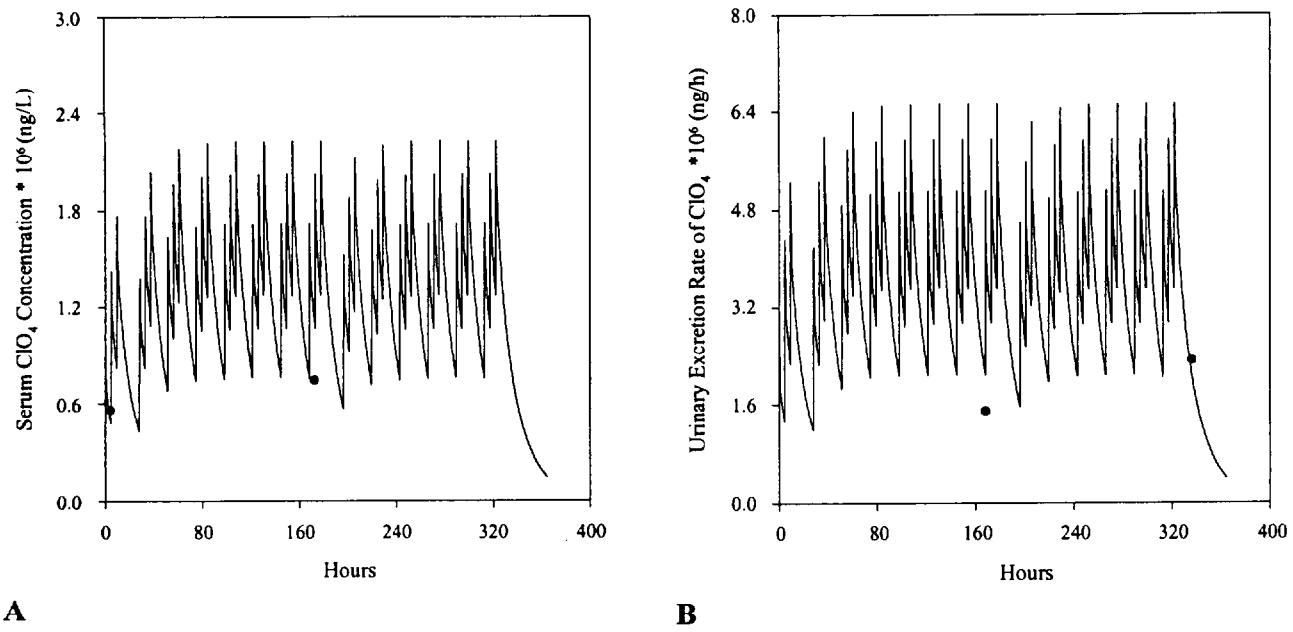

Figure 8. PBPK model predicted (solid lines) and measured values (solid circles) for serum concentrations (A) and urinary excretion rates (B) from a healthy male dosed with 1.0 mg/kg-d ClO_4, three times daily for two weeks

The model slightly overpredicted urinary perchlorate excretion rates at both the 12.0 and 1.0 mg/kg-d perchlorate dose levels. Again, an increase in the excretion rates is noted over time (Figures 7B and 8B), suggesting that perchlorate is accumulating slightly, in a fashion not described by the model. This accumulation effect is likely to account for the model's slight overestimation of serum concentrations (Figures 7A and 8A).

Because of rapid clearance, accurate dosing information is very important in simulating iodide and perchlorate kinetic data from multi dosing studies. Figure 9 compares the model predicted daily fluctuations in serum perchlorate levels from the same dose (12.0 mg ClO_4/kg-d) administered once versus 3 times per day for 2 weeks. Predicted serum concentrations ranged from approximately 0.7×10^7 to 2.7×10^7 ng/L during a 3 times per day dosing regime. Dosing once per day resulted in peak serum concentrations nearly twice as high, ranging between 0.5×10^7 and 4.2×10^7 ng/L.

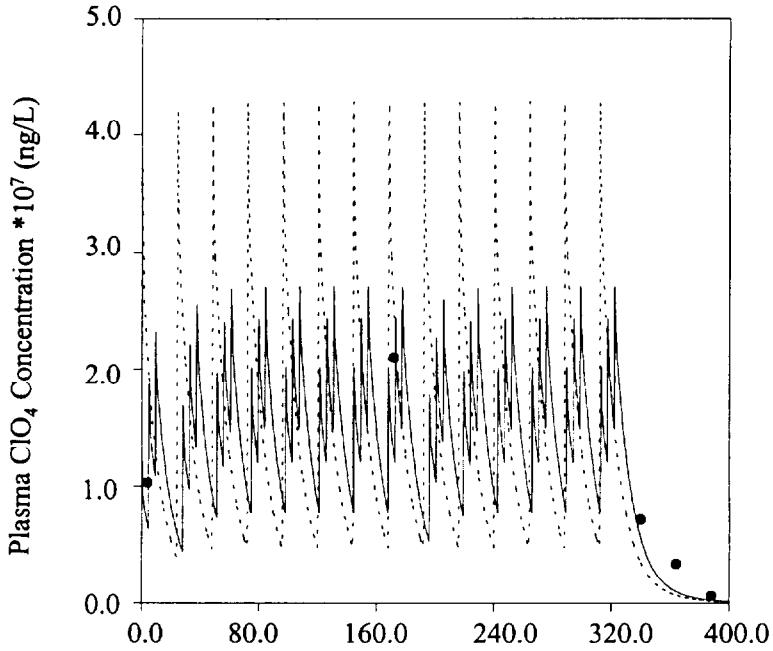

Figure 9. Model simulated serum perchlorate concentrations (solid and dotted lines) and actual values (closed circles) for one of the male volunteers in the Brabant and Leitolf study. Dotted and solid lines simulate serum concentrations if the subject drank the entire dose (12 mg/kg-d), once versus three times per day (e.g., near meal times).

3. Inhibition of Thyroid Uptake Model

Inhibition of radioiodide uptake into the thyroid after repeated exposure to perchlorate (0.14 mg/kg-d) was simulated using unpublished data from Dr. Braverman. As demonstrated in Figure 7, correct dosing information is important for simulations of iodide and perchlorate due to systemic clearance. As ingestion times were not available, it was assumed that each subject drank the perchlorate water four times per day during the waking hours.

Kuc_p values were individually fit to serum perchlorate concentration curves for each subject (Table 4). The model predicted serum perchlorate levels and urinary elimination rates, based on the average Kuc_p and the actual values, are provided in Figures 10A and B. At approximately 0.14 mg ClO_4/kg-d, the model slightly overestimates the urinary perchlorate elimination rates (Figure 10B). Twenty-four hour cumulative urine levels were highly variable (Table 5).

TABLE 4 INDIVIDUALLY FIT PARAMETERS FROM ~0.14 mg/kg-d STUDY GROUP[a]

Subject	BW (kg)	Dose Rate (ng/kg-d)	KUc_p	Vmaxc_Ti (ng/h/kg)	Ki_Ti (ng/L)	% inhibition of 8 h RAIU[b]
A	84.1	1.19E+05	0.19	9.50E+05	7.80E+06	47.2
B	79.3	1.26E+05	0.24	1.20E+06	6.50E+06	47.8
C	78.9	1.27E+05	0.25	4.50E+05	6.00E+06	41.6
D	77.3	1.29E+05	0.20	4.00E+05	4.50E+06	17.1
E	112.5	8.89E+04	0.20	6.00E+05	5.00E+06	21.8
F	77.5	1.29E+05	0.27	6.40E+05	5.50E+06	42.8
G	87.3	1.15E+05	0.21	6.50E+05	6.00E+06	40.3
H	100.4	9.96E+04	0.23	7.00E+05	4.50E+06	23.9
I	71.6	1.40E+05	0.25	1.30E+06	6.70E+06	42.8
Average	8.54E+01	1.17E+05	0.23	7.66E+05	5.83E+06	36.1

[a] Data derived from unpublished data provided by Dr. Lewis Braverman.

[b] % 8-h inhibition is not a fit parameter but represents the difference between RAIU measurements at baseline and day 14 of perchlorate, 8 h after oral administration of approximately 0.051 ng ^{123}I.

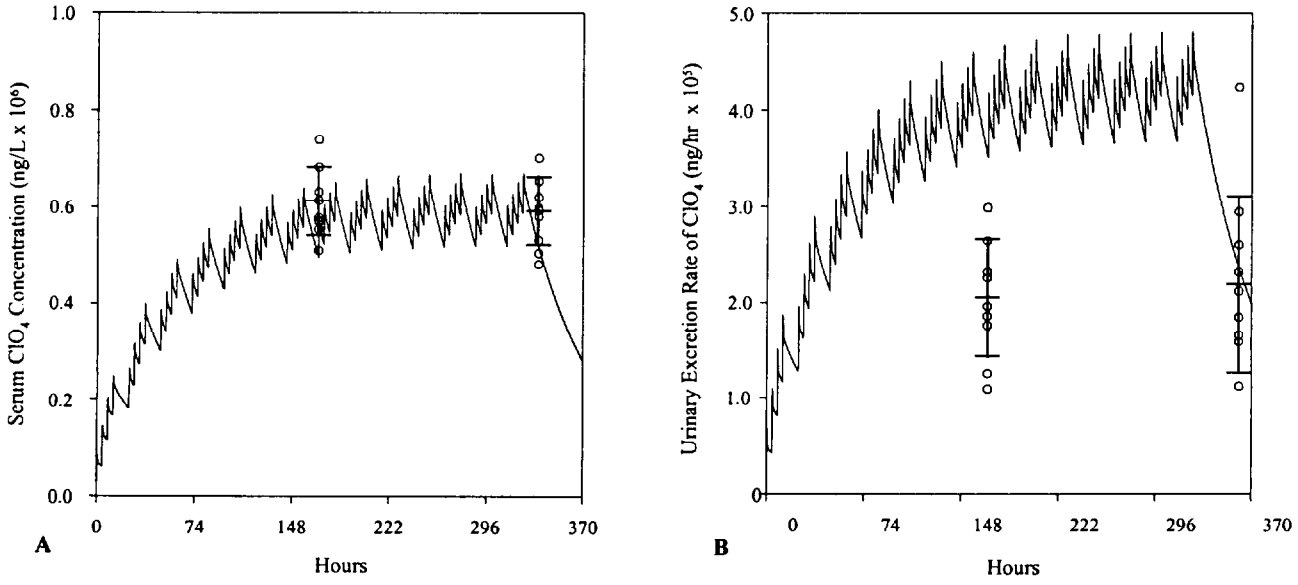

Figure 10. Model predicted (lines) and actual values (circles), including mean and s.d. (bars) of serum perchlorate concentrations (A) and perchlorate urinary excretion rates (B) of nine healthy males dosed 10 mg ClO_4/d (~0.14 mg/kg-d) for two weeks

TABLE 5. URINARY IODIDE AND PERCHLORATE AND RAIU MEASUREMENTS PREVIOUS TO AND DURING PERCHLORATE EXPOSURE

Subject	Week of Study	Total Iodide in 24-h Urine (ug)	Total ClO_4 in 24-h Urine (mg)	4-h RAIU % ^{123}I dose	8-h RAIU % ^{123}I dose	24-h RAIU % ^{123}I dose
A	Pre-ClO_4	89	<0.5	14.9	19.5	25.4
	2 wks ClO_4	269	5.9	7.7	10.3	14
B	Pre-ClO_4	212	<0.5	17.5	24.7	32.5
	2 wks ClO_4	156	10.8	9.7	12.9	15.2
C	Pre-ClO_4	700	<0.5	7.3	10.1	13.7
	2 wks ClO_4	945	10.2	4.8	5.9	6.6
D	Pre-ClO_4	323	<0.5	7.6	10.9	14.4
	2 wks ClO_4	1094	8.6	6.3	7.7	9
E	Pre-ClO_4	206	<0.5	10.3	14.2	20.2
	2 wks ClO_4	228	3.9	7.6	11.1	14.2
F	Pre-ClO_4	270	<0.5	11.8	16.3	23.6
	2 wks ClO_4	120	8.4	9.32	9.32	14.9
G	Pre-ClO_4	402	<0.5	13.5	15.4	19
	2 wks ClO_4	299	5.6	7.2	9.2	10.7
H	Pre-ClO_4	31	<0.5	10.5	18	26
	2 wks ClO_4	271	4.8	8.5	13.7	19.2
I	Pre-ClO_4	56	<0.5	18.8	26.8	37.2
	2 wks ClO_4	90	11.8	12.54	15.33	21.8
Averages	**Pre_ClO_4**	**254.3**	**<0.5**	**12.5**	**17.3**	**23. 6**
	2 wks ClO_4	**385. 8**	**7. 8**	**8.2**	**10.6**	**14.0**

After KUc_p values were estimated by fitting serum perchlorate levels from each individual, the average KUc_p, 0.23 /h (Table 4), was applied also as the elimination constant for iodide (KUc_i) for the entire dose group. In the model, thyroid iodide uptake corresponds to the RAIU data. RAIU data were then individually fitted by adjusting Vmaxc_Ti (Figure s11A through I). Km_Ti was left at the value derived from Gluzman and Niepomniszcze (1983) (3.96 x 10^6 ng/L). Vmaxc_Ti's ranged from 4 x 10^5 to 1.3 x 10^6 ng/h/kg, with an average of 7.66 x 10^5 ng/h/kg (Table 4). This value is only slightly higher than the Vmaxc_Ti, fitted from the Hays and Solomon data at 3 x 10^5 ng/h/kg.

Using the average Kuc_p and Vmaxc_Ti from Table 4, 4- and 8-h RAIU's taken on day 14 of perchlorate dosing were individually fitted by increasing the original Km_Ti (Figures 11A through I). The fitted Km value during inhibition by perchlorate is referred to as the inhibition affinity constant, Ki_Ti. Ki_Ti values ranged from 4.5 x 10^6 to 7.8 x 10^6 ng/L. The average Ki_Ti (5.83 x 10^6 ng/L) is approximately 47% higher than the affinity constant derived by Gluzman and Niepomniszcze (1983) (3.96 x 10^6 ng/L). The individually fitted parameters from this dose group are presented in Table 4.

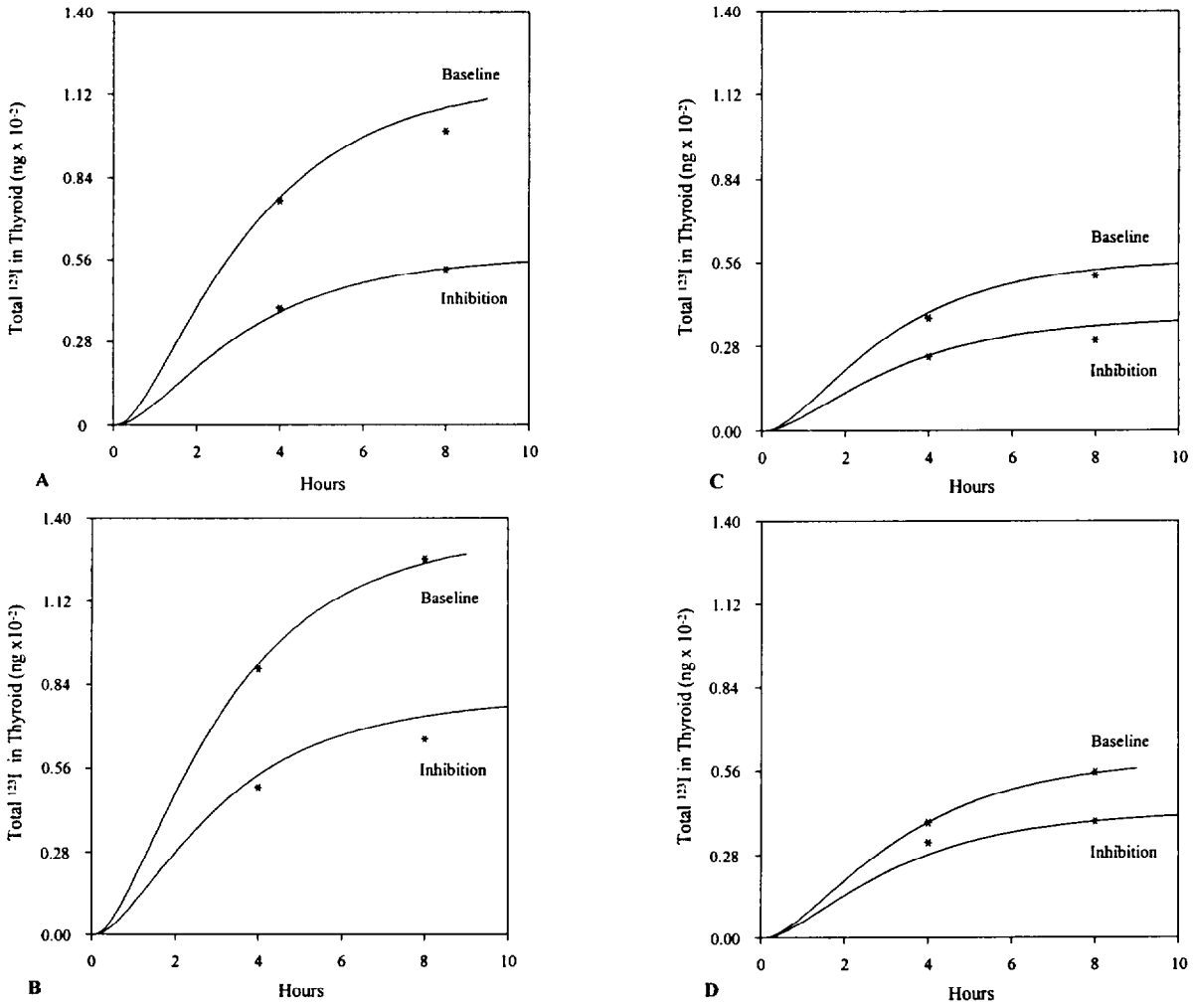

Figure 11. (continued)

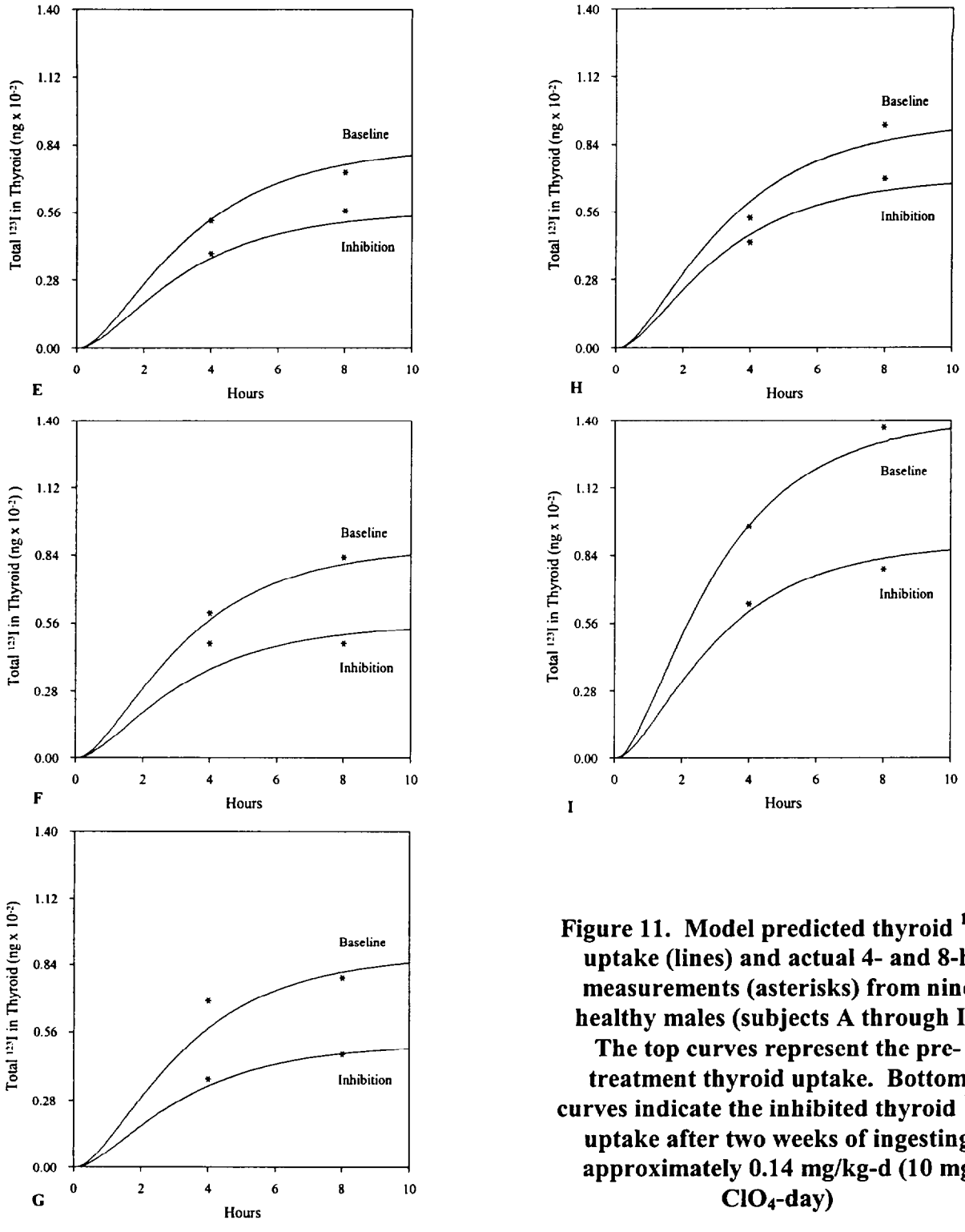

Figure 11. Model predicted thyroid ^{123}I uptake (lines) and actual 4- and 8-h measurements (asterisks) from nine healthy males (subjects A through I). The top curves represent the pre-treatment thyroid uptake. Bottom curves indicate the inhibited thyroid ^{123}I uptake after two weeks of ingesting approximately 0.14 mg/kg-d (10 mg ClO_4-day)

The average 8-h RAIU on day 14 of perchlorate was 36.1% less than pre-perchlorate RAIU measurements (Table 4). Subjects C and D exhibited the lowest RAIU levels and Vmaxc_Ti

values, both pre-treatment and on day 14 of treatment (Figures 11C and D, Tables 4 and 5). The cumulative 24-h urine total endogenous iodide levels before treatment for subjects C and D (700 μg and 323 μg, respectively) were high in comparison to the group mean (255 μg). On day 14, the 24-h total urinary iodide levels (also endogenous) for the two subjects were 945 and 1095 μg, in comparison to the group mean of 385 μg iodine. It appears the reduced thyroid ^{123}I uptake seen in subjects C and D may be a result of increased intake of dietary iodine. Endogenous serum iodide levels were not analyzed, but we would expect higher levels in these two individuals.

SUMMARY AND CONCLUSIONS

The development of the human model was based on limited human kinetic data and extrapolations made from animal studies. Some variability across data sets was noted in the mean Vmaxc_Ti values, ranging from 3.00×10^5 to 7.66×10^5 ng/h/kg. These values were estimated from visual best fits. The inhibition affinity constant (Ki_Ti) values, fitted from Braverman's 0.14 mg/kg/d perchlorate study, ranged from 4.5×10^6 to 7.0×10^6 ng/L. Other dose groups are needed to test the robustness of the model to predict inhibition of uptake of iodide in the thyroid. However, the ability of the model to simulate such a variety of studies indicates that iodide kinetics can be adequately used for perchlorate model development and vise versa.

Urinary excretion constants ranged from 0.2 to 1.1 /h across data sets; excretion constants were smaller with lower doses. At repeated low doses, the model tends to slightly underestimate serum perchlorate levels and overestimate urinary excretion rates. A slight increase in the urinary excretion rate over time was also noted. Elevated serum concentrations may indicate plasma binding of perchlorate. Yamada and Jones (1967) studied effects of different anions on plasma binding to thyroxine and noted that some of the thyroxine had been displaced after perchlorate was introduced. Thus, it could be possible that perchlorate competes with thyroxine for the same binding sites of plasma proteins. Elevated serum perchlorate levels may also account for inhibition of perchlorate uptake, in tissues other than the thyroid, by endogenous iodide which was not modeled in the simulations.

Aspects of the model, which could not be based on direct observations, were incorporated when necessary to obtain a good fit. For example, active uptake of iodide and perchlorate into human skin was incorporated in spite of a lack of available human data to support it. However, the model supports uptake in the skin. Without the skin compartment, the model overestimated circulating plasma inorganic iodide and perchlorate. The values derived from $^{36}ClO_4$ in the adult male rat (Fisher *et al.*, 2000) appear to be reasonable assumptions for iodide as well. Cutaneous uptake of iodide and perchlorate in mice and rats have also been reported by Brown-Grant and Pethes (1959) and Zeghal *et al.* (1995), respectively. The lack of reported iodide in human skin from clinical cases using radioiodide may be due to difficulty in differentiating background radioactivity. However, due to its large size, skin appears to be an important pool for slow turnover of iodide.

Dietary iodide and endogenous inorganic iodide levels are clearly important in modeling iodide and perchlorate kinetics, because excessive iodide intake can inhibit its own uptake. Plasma iorganic iodide (PII) is rarely reported in the literature, due to the difficult nature of its analysis, and it was not available in any of the studies presented in this paper. While measurements of tracer radioiodide can be fitted to predict transfer rates, its use is limited when attempting to predict the saturation of nonlinear compartments, such as the thyroid, which are dependent upon existing amount of iodide already present. Subsequent modeling efforts on predicting thyroid hormone production will require PII. Ultimately, regional dietary iodine should be considered in creating recommendations on drinking water levels for perchlorate. In addition, excessive exposure to other similarly behaving anions, such as nitrate which may be found in drinking water supplies, may contribute to antithyroid effects (Wolff and Maurey, 1963).

Human serum and urine samples from studies using different perchlorate dose levels are currently being analyzed for perchlorate and endogenous iodide and will be used to refine and validate the inhibition model. Furthermore, expansion of the model to include subsequent effects of iodide inhibition on thyroid hormone synthesis and regulation in humans is underway.

ACKNOWLEDGEMENTS

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Brabant - 12 mg/kg/d Perchlorate Serum Data
Note: Subject HL - 1 mg/kg/d

Sample	Day of Study	Serum Conc. (ppm)
PC-6	Day 1 (pre-ClO4)	0.0000
PC-5	Day 7 (pre-ClO4)	0.0000
PC-4	Day 14 (pre-ClO4)	0.0000
PC-3	Day 1 (during ClO4)	12.8403
PC-1	Day 7 (during ClO4)	14.7419
PC-2	Day 14 (during ClO4)	2.8944
PC-7	Day 15 (Recovery)	0.3709
PC-8	Day 16 (Recovery)	0.0000
WC-4	Day 1 (pre-ClO4)	0.0000
WC-5	Day 7 (pre-ClO4)	0.0000
WC-6	Day 14 (pre-ClO4)	0.0000
WC-3	Day 1 (during ClO4)	18.9088
WC-1	Day 7 (during ClO4)	34.5648
WC-2	Day 14 (during ClO4)	13.7810
WC-7	Day 15 (Recovery)	10.1093
WC-8	Day 16 (Recovery)	2.9926
KK-5	Day 1 (pre-ClO4)	0.0000
KK-6	Day 7 (pre-ClO4)	0.0000
KK-7	Day 14 (pre-ClO4)	0.0000
KK-2	Day 1 (during ClO4)	23.3765
KK-1	Day 7 (during ClO4)	55.1647
KK-3	Day 14 (during ClO4)	35.2231
KK-4	Day 15 (Recovery)	24.3301
KK-8	Day 16 (Recovery)	13.6246
NT-4	Day 1 (pre-ClO4)	0.0000
NT-6	Day 7 (pre-ClO4)	0.0000
NT-5	Day 14 (pre-ClO4)	0.0000
NT-1	Day 1 (during ClO4)	20.3885
NT-3	Day 7 (during ClO4)	21.3975
NT-2	Day 14 (during ClO4)	4.7509
NT-7	Day 15 (Recovery)	2.8696
NT-8	Day 16 (Recovery)	0.8063
WT-4	Day 1 (pre-ClO4)	0.0000
WT-2	Day 7 (pre-ClO4)	7.1316
WT-1	Day 14 (pre-ClO4)	13.7702
WT-3	Day 1 (during ClO4)	0.5883
WT-8	Day 7 (during ClO4)	0.0000
WT-5	Day 14 (during ClO4)	0.0000
WT-6	Day 15 (Recovery)	0.0000
WT-7	Day 16 (Recovery)	0.0000

Attachment 2

Brabant - 12 mg/kg/d Perchlorate Serum Data
Note: Subject HL - 1 mg/kg/d

Sample	Day of Study	Serum Conc. (ppm)
FM-5	Day 1 (pre-ClO4)	0.0000
FM-6	Day 7 (pre-ClO4)	0.0000
FM-3	Day 14 (pre-ClO4)	10.6769
FM-2	Day 1 (during ClO4)	21.3638
FM-1	Day 7 (during ClO4)	7.5276
FM-4	Day 14 (during ClO4)	3.7666
FM-7	Day 15 (Recovery)	1.0068
FM-8	Day 16 (Recovery)	0.3887
AK-4	Day 1 (pre-ClO4)	0.3157
AK-7	Day 7 (pre-ClO4)	0.3975
AK-6	Day 14 (pre-ClO4)	0.0000
AK-3	Day 1 (during ClO4)	19.7122
AK-2	Day 7 (during ClO4)	23.5687
AK-1	Day 14 (during ClO4)	6.5511
AK-5	Day 15 (Recovery)	2.1487
AK-8	Day 16 (Recovery)	0.4497

Sample		Concentration (ppm)
HL-4	Day 1 (pre-ClO4)	0.0000
HL-6	Day 7 (pre-ClO4)	0.0000
HL-5	Day 14 (pre-ClO4)	0.0000
HL-2	Day 1 (during ClO4)	0.5845
HL-1	Day 7 (during ClO4)	0.7672
HL-3	Day 14 (during ClO4)	0.0000
HL-7	Day 15 (Recovery)	0.0000
HL-8	Day 16 (Recovery)	0.0000

Brabant - 12 mg/kg/d Urine Perchlorate data
Note: subject HL - 1 mg/kg/d

Sample	[ClO4-] ppm	Day of Study	Urine vol. (ml)	Urine mg ClO4-	BW (kg)
AK 1	ND	0 (pre-ClO4)	1200		71
AK 2	ND	1 (ClO4)	900		
AK 3	462.44	7 (ClO4)	1000	462.44	
AK 4	188.14	14 (ClO4)	1200	225.768	
AK 5	147.68	15 (recovery)			
AK 6	65.62	16 (recovery)			
AK 7	1.40	17 (recovery)			
FM 1	ND	0			115
FM 2	ND	1	3000		
FM 3	ND	7	1700		
FM 4	165.31	14	2800	462.868	
FM 5	71.19	15	3450	245.6055	
FM 6	40.98	16	2070	84.8286	
FM 7	23.24	17			
NT 1	ND	0	2250		84
NT 2	ND	1	2650		
NT 3	162.58	7	2050	333.289	
NT 4	201.68	14	2550	514.284	
NT 5	54.05	15			
NT 6	34.42	16			
NT 7	27.32	17			
WC 1	ND	0			69
WC 2	1.40	1	1100	1.54	
WC 3	417.77	7	1500.00	626.655	
WC 4	378.81	14	850.00	321.9885	
WC 5	287.63	15	800.00	230.104	
WC 6	104.84	16			
WC 7	40.35	17			
KK 1	ND	0			99
KK 2	ND	1	1200		
KK 3	463.8	7	900	417.42	
KK 4	410.65	14	1300	533.845	
KK 5	208.51	15	600	125.106	
KK 6	173.32	16			
KK 7	164.93	17			
WT 1	ND	0			77
WT 2	103.63	1	2400	248.712	
WT 3	70.3	7	2300	161.69	
WT 4	20.62	14	2200	45.364	
WT 5	32.84	15	2200	72.248	
WT 6	7.83	16			
WT 7	ND	17			
PC 1	-	-			70
PC 2	69.01	1	-		
PC 3	134.97	7	1800	242.946	
PC 4	128.28	14	1600	205.248	
PC 5	126.57	15	1200	151.884	
PC 6	12.31	16			
PC 7	ND	17			

Sample	[ClO4-]	Day of Study	Urine vol. ml	Urine mg ClO4-	
HL 1	ND	0			86
HL 2	ND	1	1850		
HL 3	16.26	7	1300	21.138	
HL 4	8.68	14	2300	19.964	
HL 5	8.74	15	2300	20.102	
HL 6	0.85	16			
HL 7	ND	17			

Braverman ~0.14 mg/kg/d Perchlorate

Braverman Data 10 mg/d for 2 wks

Subj ID	Date	Wks	BW (kg)	Average Urine Total Iodine (ug/dl)	Total Volume ml	Total Iodine in Total Vol Urine (ug)	ClO4 in total vol urine (mg)	Total Serum Iodine ug/dl	Serum ClO4 (ug/ml)
A	1/18-19/99	0	84.09	3.5	2550	89	<0.5	8.0	0.0
A	1/26-27/99	1		6.7	2450	162	6.7	7	0.7482
A	2/2-3/99	2		12.8	2100	269	5.9	7.5	0.6631
A	2/16-17/99	4		11.8	2100	248	<0.5	8.5	0
B	1/11-12/99	0	79.27	12.5	1700	212	<0.5	5.5	0
B	1/19-20/99	1		13.8	1520	210	8.6	6	0.6399
B	1/26-27/99	2		9.3	1700	156	10.8	5.5	0.5897
B	2/9-10/99	4		17.5	750	131	<0.5	5.5	0
C	1/11-12/99	0	78.86	35.0	2000	700	<0.5	5.5	0
C	1/19-20/99	1		23.0	2500	575	10.8	5	0.5776
C	1/26-27/99	2		48.0	1970	945	10.2	5	0.6026
C	2/9-10/99	4		23.5	1600	376		4	0
D	1/11-12/99	0	77.73	17.0	1900	323	<0.5	6.5	0
D	1/19-20/99	1		28.3	1170	330	8.5	5.5	0.6905
D	1/26-27/99	2		72.0	1520	1094	8.6	5	0.7099
D	2/9-10/99	4		21.0	750	158	<0.5	5	0
E	1/5-6/99	0	112.45	12.5	1650	206	<0.5	5.5	0
E	1/13-14/99	1		16.0	1325	212	7.3	5.5	0.5796
E	1/20-21/99	2		22.8	1000	228	3.9	6.5	0.4913
E	2/2-9/99	4		18.0	1550	279	<0.5	6	0
F	1/18-19/99	0	77.45	10.3	2650	270	<0.5	6.5	0
F	1/26-27/99	1		6.8	1890	128	8.6	6.5	0.5629
F	2/2-3/99	2		6.5	1850	120	8.4	7.5	0.5411
F	2/16-27/99	4		3.9	3000	117	<0.5	5.5	0
G	1/5-6/99	0	87.27	36.5	1100	402	<0.5	9	0
G	1/13-14/99	1		21.5	1125	242	5.4	8.5	0.6222
G	1/20-21/99	2		21.8	1370	299	5.6	8	0.6293
G	2/9-10/99	4		43.0	950	408	<0.5	9	0
H	1/11-12/99	0	100.36	8.8	350	31	<0.5	5.5	0
H	1/19-20/99	1		12.8	930	119	2.9	6	0.5187
H	1/26-27/99	2		40.5	670	271	4.8	6.5	0.5143
H	2/9-10/99	4		17.0	700	116	<0.5	5.5	0
I	1/18-19/99	0	71.59	11.0	510	56	<0.5	6.5	0
I	1/26-27/99	1		7.1	1670	119	10.8	6	0.587
I	2/2-3/99	2		7.8	1150	90	11.8	6	0.6066
I	2/16-17/99	4		5.4	850	46	<0.5	8	0
Group Mean		Baseline		16.33	1601.11	254.33	**<0.5**	6.5	0
Group Mean		7d ClO4		15.08	1620.00	233.00	**7.73**	6.22222	0.61407
Group Mean		14d ClO4		26.81	1481.11	385.78	**7.78**	6.38889	0.59421
Group Mean		14d post ClO4		17.88	1361.11	208.78	**<0.5**	6.33333	0

Braverman ~0.14 mg/kg/d Perchlorate

Subj ID	Weeks	Date	4 Hour 123 I% UpTake	8 Hour 123 I% Uptake	24 Hour 123 I% Uptake	TSH uU/mL	T4 ug/dL	THBR	FTI	TT3 ng/dL
A	0	1/5/99	14.9	19.5	25.4	1.11	6.6	0.94	6.20	158.2
A	1	1/27/99				0.75	6.3	0.88	5.54	131.6
A	2	2/2/99	7.7	10.3	14.0	0.82	6.1	0.89	5.40	163.1
A	4	2/16/99	17.0	23.0	28.7	1.40	7.6	0.88	6.69	197.3
B	0	12/22/98	17.5	24.7	32.5	0.52	5.9	0.97	5.69	128.9
B	1	1/19/99				1.24	6.7	0.88	5.90	171.6
B	2	1/26/99	9.7	12.9	15.2	0.56	7.1	0.87	6.10	173.8
B	4	2/9/99	22.5	25.3	29.0	0.51	5.8	0.96	5.52	165.3
C	0	1/5/99	7.3	10.1	13.7	1.75	5.5	1.01	5.56	112.3
C	1	1/19/99				1.78	5.9	0.96	5.66	117.5
C	2	1/26/99	4.8	5.9	6.6	1.76	5.3	1.00	5.27	132.1
C	4	2/9/99	9.0	12.3	15.7	1.75	4.8	1.01	4.85	124.9
D	0	12/22/98	7.6	10.9	14.4	0.76	5.7	1.04	5.88	110.4
D	1	1/19/99				0.35	5.2	1.10	5.72	98.6
D	2	1/26/99	6.3	7.7	9.0	0.66	5.4	1.13	6.10	113.2
D	4	2/9/99	9.8	12.1	14.6	1.02	5.2	1.10	5.69	112.2
E	0	12/22/98	10.3	14.2	20.2	1.21	7.5	0.92	6.85	141.9
E	1	1/13/99				0.65	8.0	0.96	7.68	136.4
E	2	1/20/99	7.6	11.1	14.2	0.75	8.5	0.96	8.12	147.9
E	4	2/2/99	10.4	17.2	23.8	1.26	7.3	0.93	6.71	164.2
F	0	1/7/99	11.8	16.3	23.6	1.28	6.5	1.03	6.70	128.6
F	1	1/26/99				1.84	5.6	0.95	5.32	140.3
F	2	2/2/99	9.3	9.3	14.9	1.17	5.0	0.98	4.88	151.9
F	4	2/16/99	16.1	24.0	32.8	2.14	5.4	0.97	5.19	159.3
G	0	12/22/98	13.5	15.4	19.0	1.55	9.6	0.93	8.93	152.3
G	1	1/13/99				0.97	9.3	0.91	8.46	148.1
G	2	1/20/99	7.2	9.2	10.7	1.29	10.0	0.93	9.30	149.9
G	4	2/9/99	14.7	17.8	22.4	1.33	9.9	0.98	9.70	167.4
H	0	12/22/98	10.5	18.0	26.0	0.48	6.1	0.92	5.61	157.9
H	1	1/19/99				0.74	6.9	0.96	6.62	167.0
H	2	1/26/99	8.5	13.7	19.2	0.92	5.7	1.01	5.76	166.1
H	4	2/9/99	18.5	25.8	29.2	0.73	5.9	0.97	5.69	181.3
I	0	1/12/99	18.8	26.8	37.2	0.80	6.5	0.91	5.92	133.5
I	1	1/26/99				0.72	6.5	0.86	5.59	153.3
I	2	2/2/99	12.5	15.3	21.8	0.75	6.3	0.88	5.54	165.5
I	4	2/16/99	31.4	39.2	47.3	0.96	6.9	0.91	6.20	144.6
Group Mean		Baseline	**12.5**	**17.3**	**23.6**	**1.05**	**6.64**	**0.96**	**6.37**	**136.00**
Group Mean		7d ClO4				**1.00**	**6.71**	**0.94**	**6.28**	**140.47**
Group Mean		14d ClO4	**8.2**	**10.6**	**14.0**	**0.96**	**6.59**	**0.96**	**6.27**	**151.49**
Group Mean		14d post C	**16.6**	**21.9**	**27.1**	**1.23**	**6.51**	**0.97**	**6.25**	**157.38**